IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No: 37697-0033

Applicant(s):	Edward W. MERRILL *et al.*	Confirmation No.: 8881
Serial No.:	09/764,445	Examiner: Duc Truong
Filing Date:	January 19, 2001	Group Art Unit: 1711
Title:	RADIATION AND MELT TREATED ULTRA HIGH MOLECULAR WEIGHT POLYETHYLENE PROSTHETIC DEVICES	

DECLARATION OF ORHUN K. MURATOGLU

I, Orhun K. Muratoglu, do hereby declare as follows:

1. I am the Deputy Director of Orthopedic Biomechanics and Biomaterials Laboratory at the Massachusetts General Hospital and a faculty member at Orthopedic Surgery Department of the Harvard Medical School.

2. I received my doctorate in 1995 from the Massachusetts Institute of Technology in Polymer Science and Technology. I have been engaged in the field of materials science for over a decade. A copy of my *curriculum vitae* is attached as Exhibit 1.

3. I have reviewed the captioned application and the office actions issued by the examiner, including the final office action dated July 08, 2003 (Paper No. 19). I provide this declaration with analysis and experimental evidence in support of the arguments, made in response to office action dated April 08, 2003 (paper no. 16), to overcome the rejection of the claims.

Claim 128 is enabled by the captioned application

4. The examiner rejected claim 128[1] on enablement grounds. I am informed that the enablement requirement means that a specification must provide teachings that permit a person of skill in the art to make and use the invention without having to undertake undue experimentation. I am informed that undue experimentation would be manifest when efforts are required that are considered outside of or beyond the efforts normally expected in the field. Accordingly, routine design choices would not be considered undue experimentation, but the need to undertake comprehensive changes or extensive supplemental efforts to a disclosure would amount to undue experimentation. An extreme example of undue experimentation would be a specification that is so deficient that a person skilled in the art would have to undertake activities that amount to the act of invention itself to practice the claimed subject matter.

5. The captioned application discloses the starting materials and the production methodologies disclosed in U.S. Patent Nos. 6,017,975 (Saum '975 patent) and 6,242,507 (Saum '507 patent). Thus, the skilled artisan relying on the captioned application can produce the same cross-linked ultrahigh molecular weight polyethylene disclosed in the Saum '975 and '507 patents[2] and recited in claim 128 without the need for undue experimentation. All that claim 128 does is set forth some characterization data, and such data is just as dependent on the type of test run as it is on the nature of the composition itself.

6. In the instant situation, the product and its properties are inseparable, and different types of characterization data are a result of different types of tests being run, rather than differences in the tested composition. Thus, the data set forth in claim 128

[1] This claim is the same as claim 32 of the Saum '975 patent.

[2] For ease of reference, the citations I provide are only to the Saum '975 patent.

could be met by practice of an invention disclosed in the captioned application without having to undertake undue experimentation.

7. Claim 128 recites "A cross-linked ultrahigh molecular weight polyethylene having a swell ratio of less than about 5 and an oxidation level of less than about 0.2 carbonyl area/mil sample thickness after aging the ultrahigh molecular weight polyethylene at 70°C, for 14 days in oxygen at a pressure of about 5 atmospheres."

8. The following experiment was conducted to demonstrate that the captioned specification describes and enables the subject matter recited in claim 128. Ultrahigh Molecular Weight Polyethylene ("UHMWPE") was irradiated at 175°C to 100 kGy with an electron beam in a nitrogen atmosphere. These parameters are taught in captioned specification at page 19, lines 9-13 and page 30, lines 8-21, and original claims 83-86, and U.S. Patent No, 5,879,400 (issued from parent application U.S. application serial no. 08/600,744) at column 2, lines 45-47 and column 6, line 53 to column 7, line 15). Then, the irradiated UHMWPE was aged in an oxygen-containing pressure chamber at 70°C at 5 atm pressure for 2 weeks. Following aging, infrared analysis on the irradiated UHMWPE was performed and the oxidation levels were determined. Swell ratio testing also was performed per the Saum '975 patent (see column 7, lines 57-59).

9. This experiment provided the following data:

(a) The average maximum oxidation level, found in four irradiated UHMWPE specimens within the first 2 mm, was 0.1378 ± 0.0735 carbonyl area/mil.

(b) Swell ratio of four specimens was 3.31 ± 0.5.

10. The oxidation level was quantified as described in U.S. Patent No. 6,017,975 (see column 7, lines 47-56) and U. S. Patent No. 6,242,507 (see column 8,

lines 8-18). In this vein, the Saum '975 patent references the Nagy and Li methods (see Saum '975 patent at column 7, lines 50-52), which discloses how to determine the oxidation level. The oxidation level was calculated as the integration of the carbonyl peak between limits of 1660 and 1800 per Nagy and Li and then normalized (that is, divided) that value to the thickness of the sample in mils.

11. As set forth above in paragraph 9, practice of the disclosed invention in the experiment yielded cross-linked ultrahigh molecular weight polyethylene according to claim 128 which exhibited a swell ratio of "less than about 5" and an oxidation level of "less than about 0.2 carbonyl area/mil" sample thickness after aging at 70°C for two weeks in oxygen at a pressure of about 5 atmospheres. Therefore, it is evident from the experimental findings that the subject matter recited in claim 128 can be obtained without the need for undue experimentations by the skilled person following the teachings of U.S. Serial Nos. 09/764,445, 08/726,313 and 08/600,744.

The captioned application enables packaging and sterilizing

12. The examiner rejected claims 124 and 130 for not enabling the non-irradiative sterilization and packaging of implants, although the examiner admitted that the application does enable formation of implants themselves.

13. Sterilization and packaging are common requirements in the area of UHMWPE medical implants, and have been practiced in the field for decades. Common approaches can be divided into two basic categories, namely irradiative and non-irradiative. Non-irradiative approaches have the advantage of not creating free radicals in the finished UHMWPE medical implant.

14. Non-irradiative approaches rely upon gases, such as ethylene oxide (EtO) or steam. When using non-irradiative sterilization approaches, the implant is placed in

a permeable package that will allow the sterilizing gas, such as ethylene oxide or steam, to reach the implant while still separating the implant from the environment, where contamination would otherwise occur. This packaging and sterilization approach is schematically depicted in figures 1 and 2 of Lewis, *Medical Device Technology* 16-25 (January/February 1991) (Exhibit 2). These figures show that Et0 (ethylene oxide) or H_2O (heated to steam) permeates the package and displaces air such that the ethylene oxide or steam can sterilize the packaged implant. Accordingly, by 1991 the standard practice in the field was to place implants in air-permeable packaging and then sterilize them with a gas, such as ethylene oxide or steam.

15. The captioned application at page 11, lines 21-22 discloses the use of ethylene oxide and heat, which means the use of steam in the context of UHMWPE implants. Ethylene oxide and heat also are disclosed in parent application serial no. 08/726,313 at the bottom of page 8, and heat is disclosed in parent application 08/600,744 at page 8, lines 19-22. The Saum '975 patent at column 2, line 43 and column 6, lines 3-7 identifies ethylene oxide as a non-irradiative sterilization approach. Accordingly, the captioned application and its priority applications disclose non-irradiative sterilization approaches, such as ethylene oxide, which also are disclosed in the Saum '975 patent. The use of these gas-based approaches signifies the use of air-permeable packaging, as explained above in paragraph 14.

16. In sum, the skilled person relying on the captioned application would be able to employ non-irradiative sterilization with air-permeable packaging at least as early as the February 1996 priority date of the captioned application given that these methodologies were widely disseminated and practiced no later than 1991.

The claims are supported by the priority documents

17. I understand that the examiner denied the captioned application the benefit of priority to earlier filed applications on the grounds that the applications "are based on similar but different specification with different goals." See page 2 of the final office action. I am informed that in order to claim a priority benefit to a previously filed patent application (a "priority application"), that patent application must enable practice of the claimed subject matter, and the test for enablement is set forth above in paragraph 4. I also am informed that a priority application must contain a written description of that subject matter. I am informed that the written description requirement means that a specification must contain sufficient disclosure to show that the inventors possessed the claimed invention.

18. Enabling written support for claim 128 and packaging/sterilizing is discussed above. Below I confirm the existence of enabling written description in the priority applications for all of the claims:

CLAIM	EXEMPLARY SUPPORT IN THE '744 APPLICATION
124. A process for preparing a medical implant having an improved balance of wear properties and oxidation resistance comprising the steps of:	Improved mechanical properties are disclosed at pages 10-11 and Tables 1-6. Medical implants are disclosed at page 1, lines 3-5 and original claims 1-12. Oxidation resistance is discussed at page 3, lines 6-7, and page 23, lines 16-17.
irradiating a perform of ultrahigh molecular weight polyethylene to form free radicals;	Types of polyethylene, including ultrahigh molecular weight polyethylene, are disclosed at page 16, lines 4-7. Irradiation is disclosed at page 13, line 22. Formation of free

	radicals is a natural consequence of irradiation and results in the creation of cross-links upon recombination. See page 10, lines 14-15; page 13, line 20 to page 14, line 6; page 14, line 26 to page 15, line 5.
annealing the irradiated preform by heating in a substantially oxygen-free atmosphere at a temperature above about 150°C, for a time sufficient to recombine substantially all of the free radicals and cross-link the ultrahigh molecular weight polyethylene;	Temperatures above the melting point, including those above 150°C, are disclosed at page 4, lines 10-11; page 13, lines 14-15 and Example 3. The use of a low oxygen-containing nitrogen atmosphere in Example 3. Recombination of free radicals is discussed at page 23, lines 7-17 and original claim 2.
cooling the cross-linked preform while maintaining a substantially oxygen-free atmosphere;	Cooling in a nitrogen atmosphere is disclosed at page 25, lines 2-6. Cooling also is discussed at page 14, lines 10-15.
forming a medical implant from the cross-linked preform;	Medical implants formed from the cross-linked polyethylene disclosed at page 2, lines 6-10 and Examples 3 and 6.
packaging the medical implant in an air-permeable package; and	Packaging is a known requirement of medical implants to protect them from the environment. See Exhibit 2.

sterilizing the packaged implant using non-irradiative methods.	Sterilization, such as by heat (steam), is a known requirement for medical implants. See page 8, lines 19-22.
125. A process for preparing a medical implant having an improved balance of wear properties and oxidation resistance comprising the steps of:	Improved mechanical properties are disclosed at pages 10-11 and Tables 1-6. Medical implants are disclosed at page 1, lines 3-5 and original claims 1-12. Oxidation resistance is discussed at page 3, lines 6-7, and page 23, lines 16-17.
irradiating a preform of ultrahigh molecular weight polyethylene to form free radicals;	Types of polyethylene, including ultrahigh molecular weight polyethylene, are disclosed at page 16, lines 4-7. Irradiation is disclosed at page 13, line 22. Formation of free radicals is a natural consequence of irradiation and results in the creation of cross-links upon recombination. See page 10, lines 14-15; page 13, line 20 to page 14, line 6; page 14, line 26 to page 15, line 5.
annealing the irradiated preform by heating in a substantially oxygen-free atmosphere at a temperature above about 150°C, to cross-link the ultrahigh molecular weight polyethylene;	Temperatures above the melting point, including those above 150°C, are disclosed at page 4, lines 10-11; page 13, lines 14-15 and Example 3. The use of a low oxygen-containing nitrogen atmosphere in Example 3.

	Cross-links are discussed at page 13, lines 28-29 and page 14, line 5.
cooling the cross-linked preform while maintaining a substantially oxygen-free atmosphere;	Cooling in a nitrogen atmosphere is disclosed at page 25, lines 2-6. Cooling also is discussed at page 14, lines 10-15.
forming a medical implant from the cross-linked preform.	Medical implants formed from the cross-linked polyethylene disclosed at page 2, lines 6-10 and Examples 3 and 6.
126. A medical implant prepared according to the process of claim 124.	See discussion for claim 124.
127. A medical implant prepared according to the process of claim 125.	See discussion for claim 125.
128. A cross-linked ultrahigh molecular weight polyethylene having a swell ratio of less than about 5 and an oxidation level of less than about 0.2 carbonyl area/mil sample thickness after aging the ultrahigh molecular weight polyethylene at 70°C, for 14 days in oxygen at a pressure of about 5 atmospheres.	Improved mechanical properties are disclosed at pages 10-11 and Tables 1-6. Swell ratios that are less than 5 are disclosed at Tables 2 and 6. Minimized oxidation is discussed at page 10, last paragraph and page 22. Cross-links are discussed at page 13, lines 28-29 and page 14, line 5. Types of polyethylene, including ultrahigh molecular weight polyethylene, are disclosed at page 16, lines 4-7. Irradiation is disclosed at page 13, line 22. Temperatures

	above the melting point are disclosed at page 4, lines 10-11; page 13, lines 14-15 and Example 3. Cooling in a nitrogen atmosphere is disclosed at page 25, lines 2-6. Cooling also is discussed at page 14, lines 10-15. It is the above starting materials and production steps that result in the cross-linked ultrahigh molecular weight polyethylene. See paragraphs 7-11 above.
129. A medical implant comprising the ultrahigh molecular weight polyethylene of claim 128.	See claim 128 above. Medical implants made from cross-linked ultrahigh molecular weight polyethylene having improved mechanical properties are disclosed at page 1, lines 3-5 and original claims 1-12.
130. A process for preparing a medical implant having an improved balance of wear properties and oxidation resistance comprising the steps of:	Improved mechanical properties are disclosed at pages 10-11 and Tables 1-6. Oxidation resistance is discussed at page 3, lines 6-7, and page 23, lines 16-17.
irradiating a preform of ultrahigh molecular weight polyethylene to form free radicals;	Preforms are discussed at the paragraph bridging pages 11 and 12 and Examples 3 and 6. Types of polyethylene, including ultrahigh molecular weight polyethylene, are

	disclosed at page 16, lines 4-7. Irradiation is disclosed at page 13, line 22. Temperatures above the melting point are disclosed at page 4, lines 10-11; page 13, lines 14-15 and Example 3. Formation of free radicals is a natural consequence of irradiation and results in the creation of cross-links upon recombination. See page 10, lines 14-15; page 13, line 20 to page 14, line 6; page 14, line 26 to page 15, line 5.
annealing the irradiated preform by heating at a temperature above about 150°C, for a time sufficient to recombine substantially all of the free radicals and cross-link the ultrahigh molecular weight polyethylene;	Temperatures above the melting point, including those above 150°C, are disclosed at page 4, lines 10-11; page 13, lines 14-15 and Example 3. Recombination of free radicals is discussed at page 23, lines 7-17 and original claim 2.
cooling the cross-linked preform;	Cooling is discussed at page 14, lines 10-15 and page 25, lines 2-6.
forming a medical implant from the cross-linked preform;	Medical implants formed from the cross-linked polyethylene disclosed at page 2, lines 6-10 and Examples 3 and 6.

packaging the medical implant in an air-permeable package; and	Packaging is a known requirement of medical implants to protect them from the environment. See Exhibit 2.
sterilizing the packaged implant using non-irradiative methods.	Sterilization, such as by heat (steam), is a known requirement for medical implants. See page 8, lines 19-22.
143. A process for preparing a medical implant having improved mechanical properties, wherein the method comprises:	Improved mechanical properties are disclosed at pages 10-11 and Tables 1-6.
irradiating a polyethylene article to form free radicals; and	Types of polyethylene, including ultrahigh molecular weight polyethylene, are disclosed at page 16, lines 4-7. Irradiation is disclosed at page 13, line 22. Polyethylene articles are disclosed at the paragraph bridging pages 11 and 12 and Examples 3 and 6.
heating the polyethylene article to a temperature at or above the melting point such that the free radicals can recombine.	Temperatures above the melting point are disclosed at page 4, lines 10-11; page 13, lines 14-15 and Example 3. Recombination of free radicals is discussed at page 23, lines 7-17 and original claim 2.

As shown above, each of the pending claims find enabling written description in the '744 application, meaning that the '744 application shows possession of the claimed

invention and enables the skilled person to make and use the claimed invention without having to resort to undue experimentation. Therefore, the application is entitled to a priority date of February 13, 1996.

19. The claims also are supported by U.S. application serial no. 08/726,313, filed October 2, 1996, which incorporates by reference the '744 application. I identify exemplary support below:

CLAIM	EXEMPLARY SUPPORT IN THE '313 APPLICATION
124. A process for preparing a medical implant having an improved balance of wear properties and oxidation resistance comprising the steps of:	Improved mechanical properties are disclosed at pages 10,11, 19 and 42-43; and Tables 1-6. Medical implants are disclosed at page 1, lines 12-15 and original claims 1-12, and methods of making are disclosed in Examples 1-8. Oxidation resistance is discussed at page 3, lines 13-16 and pages 41-42.
irradiating a perform of ultrahigh molecular weight polyethylene to form free radicals;	Types of polyethylene, including ultrahigh molecular weight polyethylene, are disclosed at page 24, lines 13-19. Preforms are disclosed at page 11, second full paragraph; page 12, first full

	paragraph; and Examples 2, 3 and 6. Irradiation is disclosed at page 13, and page 22, lines 13-14. Formation of free radicals is a natural consequence of irradiation and results in the creation of cross-links upon recombination. See page 9, lines 9-26; page 12, lines 15-21.
annealing the irradiated preform by heating in a substantially oxygen-free atmosphere at a temperature above about 150°C, for a time sufficient to recombine substantially all of the free radicals and cross-link the ultrahigh molecular weight polyethylene;	Temperatures above the melting point, including those above 150°C, are disclosed at page 14, lines 2-7, and page 21, first full paragraph. The use of a low oxygen-containing nitrogen atmosphere in Example 3. Recombination of free radicals is discussed at page 14. The use of other gases and a vacuum are disclosed at page 14 and Example 13.
cooling the cross-linked preform while maintaining a substantially oxygen-free atmosphere;	Cooling in a nitrogen atmosphere is disclosed at page 25, lines 21-24. Cooling also is discussed at page 12, lines 21-24 and page 22, lines 22-28.
forming a medical implant from the cross-linked preform;	Medical implants formed from the cross-linked polyethylene disclosed at Examples 3 and 6.

packaging the medical implant in an air-permeable package; and	Packaging is a known requirement of medical implants to protect them from the environment. See Exhibit 2.
sterilizing the packaged implant using non-irradiative methods.	Sterilization is a known requirement for medical implants. See page 8, last paragraph, disclosing the use of ethylene oxide and heat (steam).
125. A process for preparing a medical implant having an improved balance of wear properties and oxidation resistance comprising the steps of:	Improved mechanical properties are disclosed at pages 10,11, 19 and 42-43; and Tables 1-6. Medical implants are disclosed at page 1, lines 12-15 and original claims 1-12, and methods of making are disclosed in Examples 1-8. Oxidation resistance is discussed at page 3, lines 13-16 and pages 41-42.
irradiating a preform of ultrahigh molecular weight polyethylene to form free radicals;	Types of polyethylene, including ultrahigh molecular weight polyethylene, are disclosed at page 24, lines 13-19. Preforms are disclosed at page 11, second full paragraph; page 12, first full paragraph; and Examples 2, 3 and 6. Irradiation is disclosed at page 13, and page 22, lines 13-14. Formation of free radicals is a natural consequence of irradiation and results

	in the creation of cross-links upon recombination. See page 9, lines 9-26; page 12, lines 15-21.
annealing the irradiated preform by heating in a substantially oxygen-free atmosphere at a temperature above about 150°C, to cross-link the ultrahigh molecular weight polyethylene;	Temperatures above the melting point, including those above 150°C, are disclosed at page 14, lines 2-7, and page 21, first full paragraph. The use of a low oxygen-containing nitrogen atmosphere in Example 3. Recombination of free radicals is discussed at page 14. The use of other gases and a vacuum are disclosed at page 14 and Example 13.
cooling the cross-linked preform while maintaining a substantially oxygen-free atmosphere;	Cooling in a nitrogen atmosphere is disclosed at page 25, lines 21-24. Cooling also is discussed at page 12, lines 21-24 and page 22, lines 22-28.
forming a medical implant from the cross-linked preform.	Medical implants formed from the cross-linked polyethylene disclosed at Examples 3 and 6.
126. A medical implant prepared according to the process of claim 124.	See discussion for claim 124.
127. A medical implant prepared according to the process of claim 125.	See discussion for claim 125.
128. A cross-linked ultrahigh molecular weight polyethylene having a swell ratio of less	Improved mechanical properties are disclosed at pages 10,11, 19 and 42-

than about 5 and an oxidation level of less than about 0.2 carbonyl area/mil sample thickness after aging the ultrahigh molecular weight polyethylene at 70°C, for 14 days in oxygen at a pressure of about 5 atmospheres.	43; Tables 1-6 and Examples 4 and 5. Oxidation resistance is discussed at page 3, lines 13-16 and Example 11. Swell ratios are disclosed at pages 45-46. See paragraphs 7-11 above.
129. A medical implant comprising the ultrahigh molecular weight polyethylene of claim 128.	Medical implants formed from the cross-linked polyethylene disclosed at Examples 3 and 6. See also the discussion for claim 128.
130. A process for preparing a medical implant having an improved balance of wear properties and oxidation resistance comprising the steps of:	Improved mechanical properties are disclosed at pages 10,11, 19 and 42-43; and Tables 1-6. Medical implants are disclosed at page 1, lines 12-15 and original claims 1-12, and methods of making are disclosed in Examples 1-8. Oxidation resistance is discussed at page 3, lines 13-16 and pages 41-42.
irradiating a preform of ultrahigh molecular weight polyethylene to form free radicals;	Types of polyethylene, including ultrahigh molecular weight polyethylene, are disclosed at page 24, lines 13-19. Preforms are disclosed at page 11, second full paragraph; page 12, first full paragraph; and Examples 2, 3 and 6. Irradiation is disclosed at page 13, and page 22, lines 13-14. Formation of free radicals is a natural

	consequence of irradiation and results in the creation of cross-links upon recombination. See page 9, lines 9-26; page 12, lines 15-21.
annealing the irradiated preform by heating at a temperature above about 150°C, for a time sufficient to recombine substantially all of the free radicals and cross-link the ultrahigh molecular weight polyethylene;	Temperatures above the melting point, including those above 150°C, are disclosed at page 14, lines 2-7, and page 21, first full paragraph. The use of a low oxygen-containing nitrogen atmosphere in Example 3. Recombination of free radicals is discussed at page 14. The use of other gases and a vacuum are disclosed at page 14 and Example 13.
cooling the cross-linked preform;	Cooling is discussed at page 12, lines 21-24, page 22, lines 22-28 and page 25, lines 21-24.
forming a medical implant from the cross-linked preform;	Medical implants formed from the cross-linked polyethylene disclosed at Examples 3 and 6.
packaging the medical implant in an air-permeable package; and	Packaging is a known requirement of medical implants to protect them from the environment. See Exhibit 2.
sterilizing the packaged implant using non-irradiative methods.	Sterilization is a known requirement for medical implants. See page 8, last paragraph, disclosing the use of

	ethylene oxide and heat (steam).
143. A process for preparing a medical implant having improved mechanical properties, wherein the method comprises:	Improved mechanical properties are disclosed at pages 10,11, 19 and 42-43; and Tables 1-6. Medical implants are disclosed at page 1, lines 12-15 and original claims 1-12, and methods of making are disclosed in Example 1-8. Oxidation resistance is discussed at page 3, lines 13-16 and pages 41-42.
irradiating a polyethylene article to form free radicals; and	Types of polyethylene, including ultrahigh molecular weight polyethylene, are disclosed at page 24, lines 13-19. Polyethylene articles are disclosed at page 11, second full paragraph; page 12, first full paragraph; and Examples 2, 3 and 6. Irradiation is disclosed at page 13., and page 22, lines 13-14. Formation of free radicals is a natural consequence of irradiation and results in the creation of cross-links upon recombination. See page 9, lines 9-26; page 12, lines 15-21. Articles are disclosed at page 11, first full paragraph and page 12, lines 6-9.

heating the polyethylene article to a temperature at or above the melting point such that the free radicals can recombine.	Temperatures above the melting point, including those above 150°C, are disclosed at page 14, lines 2-7, and page 21, first full paragraph. Recombination of free radicals is discussed at page 14.

As shown above, each of the pending claims find enabling written description in the '313 application, meaning that the '313 application shows possession of the claimed invention and enables the skilled person to make and use the claimed invention without having to resort to undue experimentation. Therefore, the application also is entitled to a priority date of October 2, 1996.

*****

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

10/6/03

Date

Orhun K. Muratoglu

Exhibit 1

Curriculum vitae of Orhun K. Muratoglu

DATE PREPARED: Friday, October 3, 2003

Name: Orhun Kamil Muratoglu, Ph.D.

Office Address: Massachusetts General Hospital
Orthopaedic Biomechanics Laboratory
GRJ 1206
Boston, MA 02114

Home Address: 5 Dana Street
Cambridge, MA 02138

E-Mail: orhun@alum.mit.edu
FAX: (617) 726 3883

Place of Birth: Erzurum, Turkey

Education:

1991 B.S. Rensselaer Polytechnic Institute, Materials Science and Engineering

1995 Ph.D. Massachusetts Institute of Technology, Materials Science and Engineering, Program in Polymer Science and Technology

Academic Appointments:

1995-2002	Instructor, Harvard Medical School, Orthopaedic Surgery
2000-present	Alan Gerry Scholar, Massachusetts General Hospital, Orthopaedic Surgery
2002-present	Assistant Professor, Harvard Medical School, Orthopaedic Surgery

Hospital or Affiliated Institution Appointments:

1995-2001 Assistant Bioengineer, Massachusetts General Hospital, Orthopaedic Surgery

1995-present Research Affiliate, Massachusetts Institute of Technology, Department of Chemical Engineering

2001-present Deputy Director, Orthopaedic Biomechanics and Biomaterials Laboratory, Massachusetts General Hospital

Professional Societies:

1990-present	Materials Research Society, Member
1990-present	American Chemical Society, Member

1995-present	American Institute of Chemical Engineers, Member
1995-present	Society for Biomaterials, Member
1996-present	American Society for Testing and Materials
1997-present	Orthopaedic Research Society, Member
2000-present	American Academy of Orthopedic Surgeons

Awards and Honors:

1989-1991 Dean's List, 4 of 4 semesters at Rensselaer Polytechnic Institute
1990-1991 Matthew Albert Hunter Prize for outstanding academic achievement at Rensselaer Polytechnic Institute
1991 Rensselaer Polytechnic Institute, Summa Cum Laude
1991-1992 PPST Fellowship sponsored by Shell and Mobil at Massachusetts Institute of Technology
1992-1994 DuPont Fellowship at Massachusetts Institute of Technology
1995 First prize, Hoechst Celanese Polymer Poster Competition at Massachusetts Institute of Technology
1995 Massachusetts Institute of Technology, Summa Cum Laude
1998 Best Paper Award – Montreal RETEC '97, Society of Plastics Engineers, Inc., "Mechanisms of Deformation and Toughness in Rubber-Modified Semicrystalline Thermoplastics"
1999 'HAP' Paul Award – International Society for Technology in Arthroplasty 1999 Meeting, "A Novel Method of Crosslinking UHMWPE to Improve Wear, Reduce Oxidation and Retain Mechanical Properties"
2000 2000 Partners In Excellence Award for excellence in leadership, innovation, and teamwork.
2001 Marshall R. Urist Young Investigator Award for 2001, "A Highly Crosslinked, Melted UHMWPE: Expanded Potential for Total Joint Arthroplasty"

Invited Presentations:

Invited Lectures, Massachusetts Institute of Technology, Summer Professional Course on 'Toughening of Polymers: Mechanistic Principles, Experiments and Modeling,' Boston, Massachusetts, 1995

Invited Lecture, Workshop on Polyethylene, Combined Orthopaedic Research Society, San Diego, California, 1995

Plenary Lecture, 1998 Gordon Conference on Tribology, New Hampshire, 1998

Invited Lecture, Material Science and Engineering Colloquium Series, Ohio State University, Ohio, 1998

Invited Lecture, Mechanical Engineering, Aeronautical Engineering and Mechanics, Rensselaer Polytechnic Institute, Albany, New York, 1999

Invited Lecture, Hip, Knee and Shoulder Symposium, Park City, Utah, 1999

Invited Lecture, Biomechanics Seminar Series, Boston University, Boston, Massachusetts, 1999

Invited Lecture, European Knee Osteoarthritis Week, Arthroplasty Symposium, Ulm Germany, 2000

Grand Rounds, Carney Hospital, Dorchester, Massachusetts, 2000

Invited Lecture, 2nd Harlaching Spring Symposium, Munich, Germany, 2000

Invited Lecture, Whistler 2000 Orthopaedic Symposium, Whistler, British Columbia, Canada, 2000

Invited Lecture, Orthopaedic Research Society, Wear 2000 Workshop, Orlando, Florida, 2000

Invited Lecture, 2000 Hip, Knee and Shoulder Symposium, Park City, Utah, 2000

Invited Lecture, American Academy of Orthopaedic Surgeons and National Institute of Health (AAOS/NIH), Wear 2000 Workshop, Oak Brook, Illinois, 2000

Invited Lecture, Italian Society of Orthopedics and Traumotology, 85th National Congress, Torino, Italy, 2000

Invited Lecture, The 27th Annual Meeting of the Japanese Hip Society, Nagoya, Japan, 2000

Invited Lecture, Triennial Congress of the Asian Pacific Orthopaedic Association, Adelaide, South Australia, April 1-6, 2001

Invited Lecture, Workshop on Ultra-High Molecular Weight Polyethylene, Society for Biomaterials, 27th Annual Meeting, St. Paul Minnesota, April 24, 2001.

Invited Lecture, New Test Methods for Evaluating the Performance of Conventional and Crosslinked UHMWPE at the American Society for Testing and Materials, Quantification of Radiation Dose for UHMWPE, Phoenix, AZ, May 8, 2001.

Invited Lecture, Der Osteoblast 2001, Osteologie in Forschung und Praxis, Wurzburg, Germany, November 17, 2001.

Invited Keynote Lecture, Tribology Issues in Biology and Medicine, Argonne National Laboratory, Argonne, Illinois, December 10-12, 2001.

Grand Rounds, University of Utah, University Hospital, Salt Lake City, Utah, January 16, 2001.

Invited Lectures, The 2002 Hip, Knee, and Shoulder Symposium, Park City, Utah, March 6-10, 2002.

Invited Lecture, The Third Annual Turkish Arthroplasty Meeting, Antalya, Turkey, September 16, 2002.

Grand Rounds, University of Oklahoma College of Medicine, Department of Orthopedic Surgery and Rehabilitation, Oklahoma City, Oklahoma, October 25, 2002.

Invited Lecture, New England Orthopedic Society Fall Meeting, November 23, 2002.

Invited Lectures, 2003 Hip, Knee and Shoulder Symposium, Park City, Utah, 2003.

Invited Lecture, 2003 European Orthopaedic Research Society Satellite Symposium, Helsinki, Finland, June 4-7, 2003.

Invited Lecture, 2003 European Federation of National Associations of Orthopaedic and Traumatology, Helsinki, Finland, June 4-10, 2003.

Bibliography:

Original Articles:

Muratoglu, OK, Cohen, RE, Argon, AS, and Weinberg, M., 'Microstructural Fracture Processes Accompanying Growing Cracks in Tough Rubber-Modified Polyamides,' Polymer, **36**(25): 4787, (1995).
Muratoglu, OK, Cohen, RE, Argon, AS, and Weinberg, M., 'Microstructural Processes of Fracture of Rubber Modified Polyamides,' Polymer, **36**(25): 4771, (1995).
Muratoglu, OK, Cohen, RE, and Argon, AS, 'Crystalline Morphology of Polyamide 6 Near Planar Surfaces,' Polymer, **36**(11): 2143, (1995).
Muratoglu, OK, Cohen, RE, Argon, AS, and Weinberg, M., 'Toughening Mechanism of Rubber Modified Polyamides,' Polymer, **36**(5): 921, (1995).
Muratoglu, OK, Jasty, M, and Harris, WH, 'A New Method to Determine the Locus of Radiation Damage in Retrieved UHMWPE Components,' ASTM-STP **1307**:79, (1997).
Muratoglu, OK, Bragdon, CR, O'Connor, DO, Jasty, M, and Harris, WH, 'Unified Wear Model for Highly Crosslinked Ultra-High Molecular Weight Polyethylenes (UHMWPEs),' Biomaterials, **20**(16): 1463, (1999).
Muratoglu, OK, Bragdon, CR, O'Connor, DO, Jasty, M, and Harris, WH, 'A Novel Method Of Crosslinking UHMWPE To Improve Wear, Reduce Oxidation And Retain Mechanical Properties,' Journal of Arthroplasty, **16**(2), 149-160, (2001).
Kurtz, SM, Muratoglu OK, Buchanan, FJ, Currier, B., Gsell, R, Greer, K, Gualtieri, G., Johnson, R, Schaffner, S, Sevo, K., Spiegelberg, SH, Shen, FW, and Yau, SS, 'Interlaboratory Reproducibility of Standard Accelerated Aging Methods for Oxidation of UHMWPE,' Biomaterials, **22**(13), 1731-1737, (2001).
Kurtz, SM, Muratoglu OK, Buchanan, FJ, Currier, B., Gsell, R, Shen, FW, and Yau, SS, 'Interlaboratory Studies to Determine Optimal Analytical Methods for Measuring the Oxidation Index of UHMWPE,' Biomaterials, **22**(21), 2875-2882, (2001).
Muratoglu, OK and Harris, WH, 'Identification and Quantification of Irradiation in UHMWPE Through Trans-Vinylene Yield,' Journal of Biomedical Materials Research, **56**(4): 584-592, (2001).
Kurtz, SM, Muratoglu OK, Gsell, R, Greer, K., Shen, FW, Cooper, C., Buchanan, FJ, Spiegelberg, SH, Yau, SS, and Edidin, AA 'Interlaboratory Validation of Oxidation-Index Measurement Methods for UHMWPE after Long-Term Shelf Aging,' Journal of Biomedical Materials Research (Applied Biomaterials), **63**(1): 15-23, (2001).
Muratoglu, OK, O'Connor, DO, Bragdon, CR, RS, Perinchief, Estok, DM, Jasty, M, and Harris, WH, 'A New Concept: Larger Diameter Femoral Heads used in Conjunction with a Highly Crosslinked UHMWPE,' Journal of Arthroplasty, **16**(8) Supplement, 24-30, (2001).
Duffy, GP, Muratoglu OK, Biggs, SA, Larson, SL, Lozynsky, AJ, and Harris, WH, 'A Critical Assessment of Proximal Macrotexturing on Cemented Femoral Components,' Journal of Arthroplasty, **16**(8) Supplement, 42-48, (2001).

Muratoglu, OK, O'Connor, DO, Bragdon, CR, Delaney, J, Jasty, M, Harris, WH, Merrill, E, and Venugopalan, P, 'Gradient Crosslinking of UHMWPE Using Irradiation in Molten State for Total Joint Arthroplasty,' Biomaterials, **23**(3): 717-724 (2002).
Muratoglu. OK, Bragdon, CR, O'Connor, DO, Perinchief, RS, Jasty, M, and Harris, WH, 'Aggressive Wear Testing of a Cross-linked Polyethylene in Total Knee Arthroplasty,' Clinical Orthopaedics and Related Research, **404**:89-95, (2002).
Muratoglu OK, Mark A, Vittetoe DA, Harris WH, Rubash HE, 'Polyethylene Damage in Total Knees and Use of Highly Crosslinked Polyethylene,' Journal of Bone and Joint Surgery, **85-A**(Supplement 1):7-11, (2002)
Muratoglu. OK, Delaney, J, O'Connor, DO, and Harris, WH, 'The Use of Trans-vinylene Formation in Quantifying the Spatial Distribution of Electron Beam Penetration in Polyethylene. Single-Sided, Double-Sided and Shielded Irradiation' Biomaterials, **In Print**, (2003).
Muratoglu. OK, Perinchief, RS, Bragdon, CR, O'Connor, DO, Konrad, R, and Harris, WH, 'Metrology to quantify wear and creep of polyethylene tibial knee inserts,' Clinical Orthopaedics and Related Research, **410**: **155-164** (2003).
Bragdon CR, Jasty M, Muratoglu OK, O'Connor D, Harris WH, 'Third Body Wear of a Highly Crosslinked Polyethylene in a Hip' Journal of Arthroplasty, **In Print**, (2003).
Gul RM, McGarry FJ, Bragdon CR, Muratoglu OK, Harris WH, 'Effect of consolidation on adhesive and abrasive wear of ultra-high molecular weight polyethylene,' Biomaterials, **24**(19): 3193-3199, (2003).
Muratoglu OK, Ruberti J, Melotti S, Spiegelberg SH, Greenbaum ES, Harris WH, 'Optical Analysis of Surface Changes on Early Retrievals of Highly Crosslinked and Conventional Polyethylene Tibial Inserts,' The Journal of Arthroplasty, (AAHKS supplement): **In Print,** (2003).
Muratoglu OK, Merrill EW, Bragdon CR, O'Connor DO, Hoeffel D, Burroughs BR, Jasty M, Harris WH, 'Effect of Radiation, Heat, and Aging on in Vitro Wear Resistance of Polyethylene,' Clinical Orthopaedics and Related Research, **In Print,** (2003).
Muratoglu, OK, Greenbaum, ES, Bragdon, CR, Jasty, M, Freiberg, AF, Harris, WH 'Surface Analysis of Early Retrieved Acetabular Polyethylene Liners: A Comparison of Conventional and Highly Crosslinked Polyethylenes,' Journal of Arthroplasty, **In Print**, (2003).

Proceedings of Meetings – Full Articles

Argon, AS, Bartczak, Z, Cohen, RE, Muratoglu, OK, 'Novel Mechanisms of Toughening Semi-Crystalline Polymers,' Proc. 18th Riso International Symposium on Materials Science: Polymeric Composites - Expanding the Limits, Eds: Andersen, SI, Brondted, P, Lillhot, H, Lystrup Aa, Rheinlander JT, Sorensen, BF, and Toftegaard, H, Riso National Laboratory, Roskilde, Denmark, (1997).

Reviews, Chapters, and Editorials:

Argon, AS, Cohen, RE, and Muratoglu, OK, 'Toughness of Particle Modified Semi-Crystalline Polymers: General Principles and Specific Examples,' in Mechanics of Plastics and Plastic Composites, ed. M. C. Boyce, ASME Publication, New York, pp: 177-196, (1995).
Kurtz, SM, Muratoglu, OK, Evans, M, Edidin, AA, Advances in the Processing, Sterilization, and Crosslinking of Ultra-High Molecular Weight Polyethylene for Total Joint Arthroplasty, Biomaterials, **20**(18): 1659-1688 (1999).
Argon, AS, Bartczak, Z, Cohen, RE, Muratoglu OK, 'Novel Mechanisms of Toughening Semi-Crystalline Polymers,' in Toughening of Plastics, Advances in Modeling and Experiments, eds. Pearson RA, Sue H-J, and Yee, AF, ACS Symposium Series 759, American Chemical Society, Washington D.C., pp: 98-124 (2000).

Muratoglu, OK, Bragdon, CR, O'Connor, DO, Jasty, M, Harris, WH, in A Highly Crosslinked, 'Melted Ultra-High Molecular Weight Polyethylene: Expanded Potential for Total Joint Arthroplasty,' World Tribology Forum in Arthroplasty, Eds. Rieker, C, Oberhaulzer, S, and Wyss, U, Hans Huber, Bern, pp: 245-262 (2001).

Muratoglu, OK and Kurtz, SM, 'Alternate Bearing Surfaces in Hip Replacement,' in Total Hip Replacement: Current Trends and Controversies, ed. Sinha, RK, Marcel Dekker, New York, pp: 1-46, (2002).

Muratoglu, OK, and Harris, WH, 'Use of Highly Crosslinked UHMWPE in THR to Decrease the Generation of Wear Debris and Reduce Periprosthetic Osteolysis,' in Seminars in Arthroplasty, eds. Illgen, R and Rubash, HE, W. B. Saunders, Harcourt Health Sciences Co. Vol 13, No 4, pp: 318-324 (2002).

Muratoglu, OK, Deluzio, K, Rubash, HE, Harris, WH, 'The Use of High Dose Irradiated and Melt Treated UHMWPE in TKR to Decrease the Incidence of Delamination and Wear Debris Generation,' in Seminars in Arthroplasty, eds. Illgen, R and Rubash, HE, W. B. Saunders, Harcourt Health Sciences Co. Vol 13, No 4, pp: 338-343 (2002).

Muratoglu, OK and Harris, WH, 'Electron Beam Crosslinked and Melted Polyethylene in Total Hip and Knee Arthroplasty,' in Joint Replacement and Bone Resorption: Pathology, Biomaterials, and Clinical Practice, eds. Shanbagh, AS, Rubash, HE, and Jacobs, JJ, Marcel Dekker, New York, **In Print**, (2002).

Muratoglu, OK, Mark, AK, Harris, WH, and Rubash, HE, 'Electron Beam Crosslinked and Melted Polyethylene Should be Used in Total Knee Replacements,' AAOS Bulletin, June 2002, pg 50-51.

Santavirta, S, Böhler, M, Harris, WH, Konttinen, YT, Lappalainen, R, Muratoglu, O, Rieker, C, Salzer, M, 'Improvement of THR Tribology. Different Solutions Available,' Acta Scandinavia, In Print, (2002).

Konrad R, Rieker C, Schon R, Muratoglu O, Perinchief R, 'A New Measurement Method for Wear Scars Generated with Knee Simulators' in Friction, Lubrication, and Wear of Artificial Joints, ed: Hutchings IM, Professional Engineering Publishing, 127-132, (2003).

Muratoglu, OK, Vittetoe, DA, and Rubash, HE, 'Damage of Implant Surfaces in Total Knee Arthroplasty,' in The Adult Knee, eds. Callaghan, JJ, Rosenberg, AG, Rubash, HE, Simonian, PT, Wickiewicz, TJ, Lippincott Williams and Wilkins, Philadelphia, 297-313, (2003).

Burroughs, BR, Muratoglu, OK, Rubash, HE, Estok, D, Jasty, M, Freiberg, AF, Harris, WH 'Development of a New In Vitro Patella Wear Tester in the Orthopaedic Biomechanics and Biomaterials Laboratory' in The Orthopaedic Journal at Harvard Medical School, 102-103, (2003)

Books, Monographs, and Text Books:

Muratoglu OK et al., Implant Wear in Total Joint Replacement: Clinical and Biological Issues, Materials and Design Considerations, Published by American Academy of Orthopaedic Surgeons, Rosemont, IL, (2001).

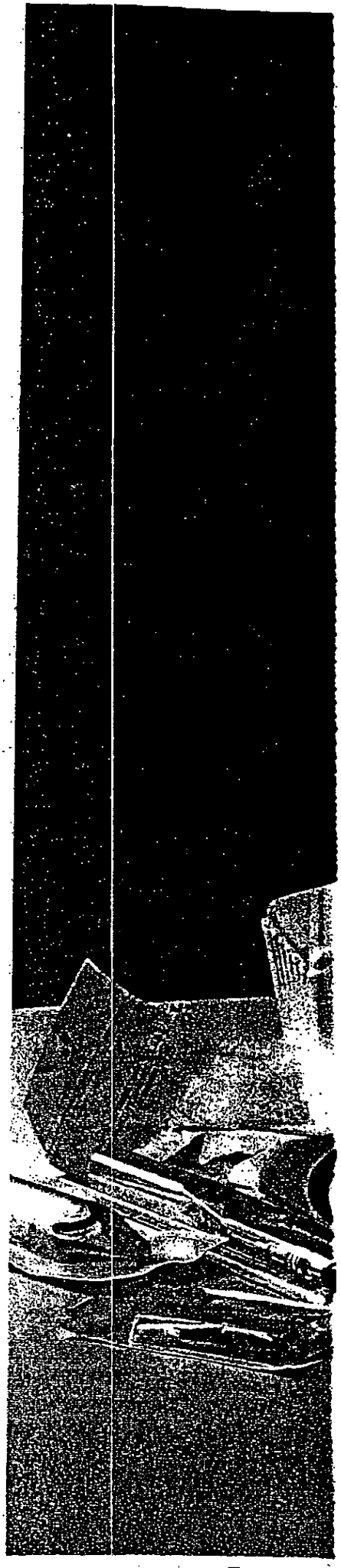
Packaging Matters — Part I: Design of the Pack

Robin Lewis
Perfecseal Ltd.,
Springtown Industrial Estate,
Londonderry BT48 OLY, United Kingdom

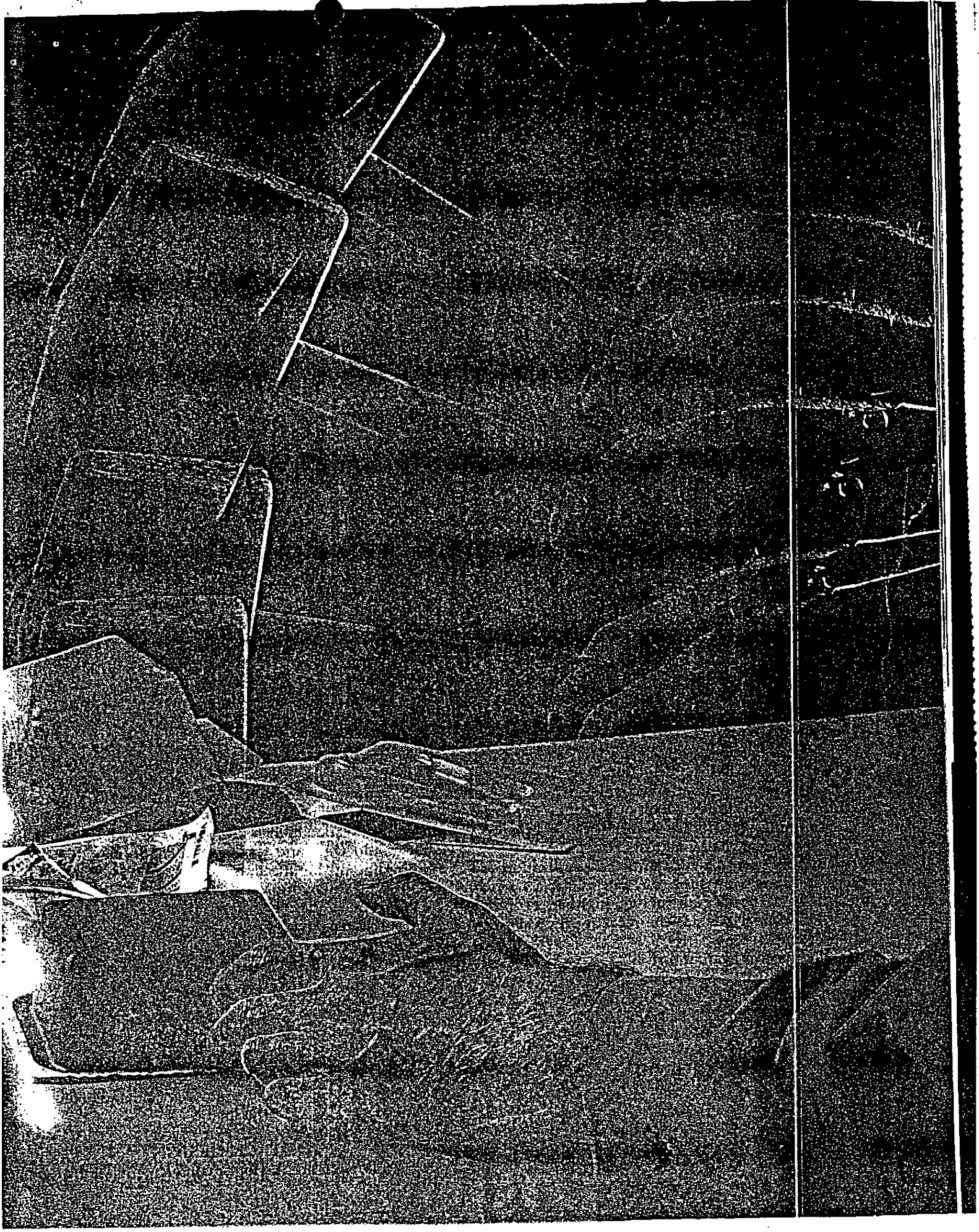
Following the author's discussion of seals and seal integrity in medical packaging in the May/June issue of Medical Device Technology, *this article discusses the parameters involved in the design of a pack. These parameters are discussed in relation to each integral part of the overall medical device package, from the inner pack to the shelf pack, and the conclusion is reached that a number of pitfalls could be avoided if the device and the package were designed together. Part II will deal with material selection.*

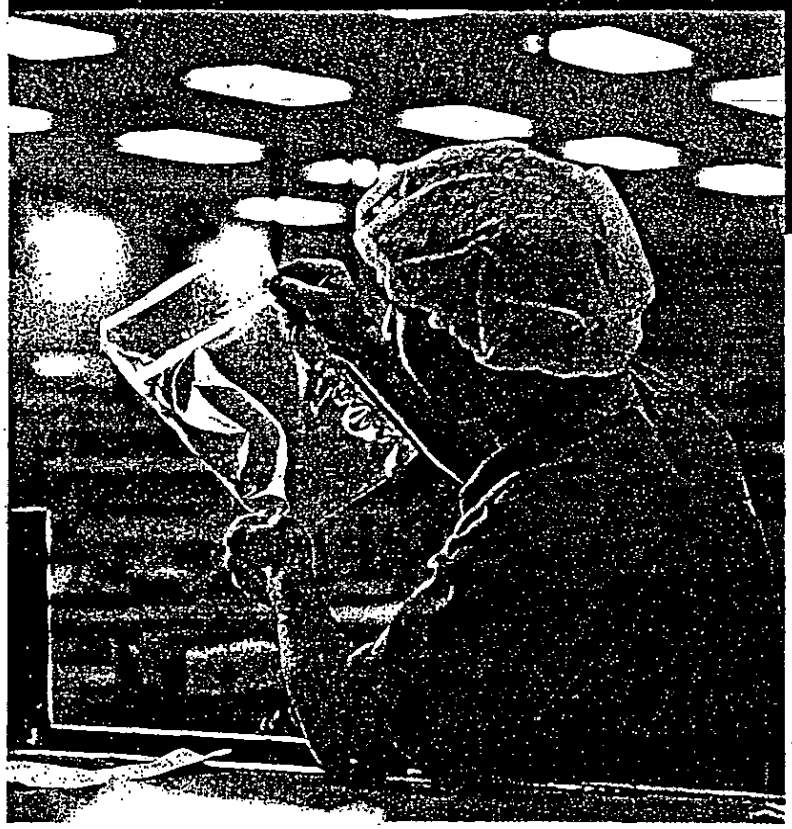
INTRODUCTION

If the medical device industry heeded its own recommendations, there would be no need for this article.



DAVID LOVEALL





COURTESY OF PERPECSEAL LIMITED

In March 1981, the Medical Disposable Sterile Packaging Association (MEDISPA) — now under the banner of the European Confederation of Medical Device Suppliers Association (EUCOMED) — published its recommendations for packaging and labelling. These recommendations cover all the problems that are likely to face those working in the field of medical packaging, yet I have not once seen this document on a packaging engineer's desk. The checklist for pack design in MEDISPA's recommendations covers such areas as

- confirmation of the suitability of a material for preconditioning and sterilization,
- microbiological challenge tests,
- label application to withstand the sterilization process and long-term storage,
- features of the pack material that might affect or damage the product, such as chemical or physical migration of constituents,
- journey hazard evaluation,
- aseptic removal,
- stability for handling and palletization, and
- providing space for clear labelling with batch-number bar code and instructions for use.

BACKGROUND

Despite the fact that the pack is an integral part of a medical device and, in the case of low-cost devices such as suction catheters, packaging costs are frequently on a par with the device costs, the time spent on the design and testing of the pack is often limited and left until the product design has been completed. This approach can result in numerous problems, such as

- incorrect material choice,
- poor pack design,
- incorrect package sealing and machine choice,
- initial sterilization failures/damage,
- delayed product launch, and
- inflated costs.

Such problems can be avoided if the pack and the device are designed and developed at the same time. For example, handling and sterilization of the pack at the prototype stage in the development of the medical device could highlight weak points in the outer shape of the package or detect *dead spots* during the sterilization cycle.

Sterilizing a handful of products in a tray is very different from sterilizing a complete pallet load of inner-wrapped and outer-packed products where orientation on the pallet and in the sterilizer-can have varying effects. (See Figures 1 and 2.) The *full* pallet must be imitated by mocking up one complete carton unit and stacking this in the most vulnerable position on a pallet with simulation of both weight and surrounding characteristics.

This article attempts to show how the combined development of package and device can save both time and money. Product design has a major effect on pack design and the gauge of material required for the package. Injection mouldings, for example, should be viewed in relation to their position in the packs and general mould wear and tear, such as split lines (the dividing line of the injection mould) and injection sites wearing and leaving sharp ridges or high spots that can protrude and cause surprising damage to the packaging materials over time.

Also, by performing transit tests at the earliest possible opportunity, those areas of the product that are likely to be problematic in relation to the package will be highlighted, such as push-fits of connectors that can become loosened, and exit angles of connectors into coiled tubing that can push against the blister lid during sterilization and cause excess pressure on the seal, which is vulnerable during sterilization. Early mock-ups can save the packaging and device manufacturers both money and embarrassment.

THE PACK DESIGN

The following are the four main elements of the device pack:

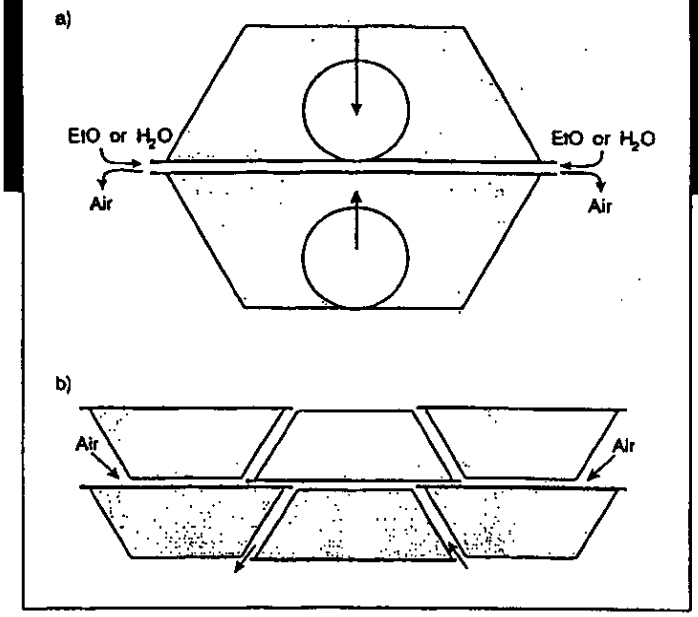


Figure 1: *Blister orientation. a) Placing of permeable lid directly against permeable lid reduces flow of air and sterilant. Escaping air seals lids together. b) Pathways around blister packs allow for easier flow of air and sterilant.*

- Inner pack: used for devices that require a double pack, such as operating-theatre devices. Inner packs generally take the form of a smaller copy of the unit container, such as a blister inside a blister, pouch inside a pouch, or a polyethylene or glassine bag.
- Ancillary components: those components that are packaged with the device, such as backing card, preformed supports, needle guards, leaflets, or inserts.
- Unit/sterilization container: the main package containing an individual device or number of devices that together make up a procedural kit. This pack must maintain the sterility and integrity of the contents until they are used. It must also permit aseptic removal of the contents and, once opened, must not be resealable.
- Shelf/multiunit container: this is the package containing a number of unit containers and offering physical protection during the normal life cycle of the device.

INNER PACK

Because this part of the pack is considered sterile, it is normally kept in place until just before the device is used. The inner pack should facilitate easy and controlled withdrawal of the device and be nonshredding as well as compatible with the contents. There is no necessity to provide labelling and information on the inner pack, unless opening instructions are deemed to be desirable, and a smaller version of the unit blister pack or pouch is considered the ideal design.

When polyethylene bags are used as inner packs, the bag frequently sticks to the device. This can be countered by using a suitable gauge of polyethylene that provides the required stiffness along with either a perforation down the length of the package or side-weld bags made from two webs sealed down the side, allowing easy removal of the device.

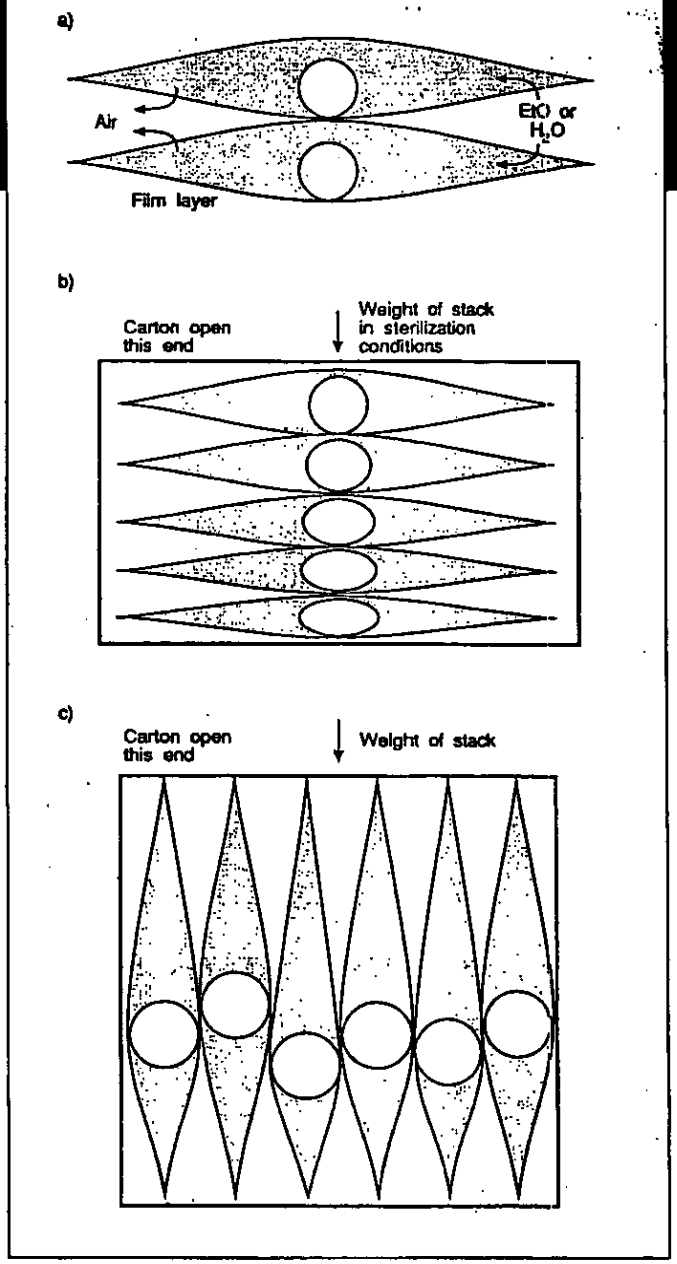


Figure 2: *Pouch orientation in carton and sterilizer alters pressure points on products. a) Permeable layers in contact do not obstruct flow because of ballooning pushing packaging apart. b) Cartons stacked vertically with products directly one over another can cause distortion in warm or hot conditions when plastic is soft. c) Products packed and stacked on edge protect each other.*

ANCILLARY COMPONENTS

Some ancillary components are required for the protection of delicate parts of a medical device, such as spe-

COURTESY OF PERFECSEAL LIMITED

cialized catheter tips that are often protected through the use of formed-plastic inserts or insert cards. The great difficulty in respect of such protective components is finding a suitable and foolproof means of holding the device without causing it damage.

Channels with undercuts are generally used with the formed plastic, and holding flaps can be introduced into the insert card if they are made of a suitable and nonshredding material. All manner of needle guards have been used — from injection mouldings to both straight and ribbed extruded tubing.

UNIT/STERILIZATION CONTAINER

The design of the unit/sterilization container takes most of the time and energy of the packaging engineer, as material or seal failure in this container can lead to loss of sterility. The unit container also carries the device manufacturer's quality image into the hospital and operating theatre. Confidence with the product's condition and success in its use is set by the initial pack appearance, its feel, and its function during the opening process.

There are three elements in the unit/sterilization container:

- blister pack: a thermoformed tray with sealed liddings;
- peel pouch: consisting of two components — a film front and a paper or Tyvek back; and
- polyethylene bag, breather bag, or patch bag: either a straightforward polyethylene bag with a tear-open feature; a specialized polyethylene bag made from two webs welded at the side and sealed to a peel strip of Tyvek; or a polyethylene bag with Tyvek disks sealed over holes to allow for gas sterilization, with a tear-open weak line built in.

Blister/thermoformed pack. The reduced volume of the three-dimensional blister pack when compared with the pouch pack makes it appear very attractive to both marketing personnel and hospital administrators who are very conscious of the necessity to save shelf space. However, there are a number of disadvantages associated with the use of this type of package, such as

- production speeds approximately 25–30% slower on thermoform-and-fill;
- larger quantities of materials required to enable a realistic production payback period;
- greater personal skills needed for the thermoforming "art";
- greater care required when sealing porous lidding materials in order to produce a clean peel with adhesive-coated materials or minimal fibre lift with uncoated materials;
- heat having to be applied to the lidding surface, which creates the possibility of the sealant layer melting too far into the porous material, resulting in weak seals or material breakdown during the peeling operation.

The last of these requirements applies equally to an adhesive coating on the lidding material or to an uncoated material that relies on the polyethylene or polypropylene layer of the thermoformed web as the sealant. The result with nonporous materials can be a squashing effect that effectively reduces the seal strength.

If the volume of the pack is reduced to a point where the product can push against the lid as the packs come out of the sealing head, the lidding can be pushed away from the seal flange, causing separation because the sealant layer is still warm and tacky. Seal lift can also be caused if the pack is not fully formed and the product pushes against the lid.

There are particular disadvantages associated with using paper lidding material, especially when this material is uncoated. The pack can become orientated in such a way that the main peel operation becomes

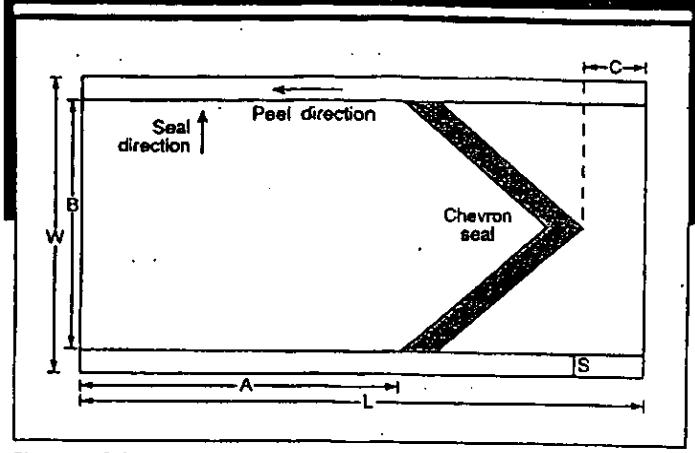


Figure 3: *Schematic representation of pouch pack where A = internal length, L = overall length, B = internal width, W = overall width, C = peel flap, and S = seal width.*

aligned with the cross direction of the paper lid. When uncoated paper is used, seals made in the cross direction are weaker than those made in the machine direction. Seal checks also need closer attention, although this need is not so great when Tyvek-film lidding is used, even though seal strengths have still been found to be different.

When gas or steam sterilization is used, permeability of the lidding material is of paramount importance in order that the easy evacuation of air and permeation of the sterilant be permitted. The blister pack has a comparatively small porous lid-to-pack volume compared to the pouch, which can increase strain on the seals and cause ballooning as the air is evacuated. Checking the evacuation rate from the pack — by testing mock-ups in an evacuation chamber — is a vital part of pack design, as long as test conditions are as realistic as possible. Testing a single layer of packs is useless; it is far better to put the packs in a carton or similar confined space that replicates production conditions as closely as possible.

Self-adhesive labels can reduce permeability quite considerably, especially when the CEN recommendations for multilingual information necessitate an increase in the size of such labels.

Too close a contact between a highly-plasticized device, such as a cuff or balloon, and an unplasticized tray can also cause problems. Contact over a five-year shelf-life can cause migration of the plasticizers and a subsequent loss of flexibility.

Male forming of preformed semirigid trays causes the seal flange to be the thinnest and most variable area of the whole pack. Remember always that the seal is the most vulnerable point of a pack: it must allow easy access via a peeled lid at the time of use, while remaining intact during a punishing sterilization process and a storage period of up to five years. During its life cycle, the atmosphere around the pack is likely to change from hot to cold, causing expansion and contraction of the air contained within it; variations in external pressure can also occur when the store cupboard or packing drawer is closed, and loading accidents — such as the accidental dropping of a pallet — can push the product against the seal.

Whenever possible, thermoformed trays should be female moulded, with clamps around the proposed seal flanges. This will ensure that the flanges remain the same gauge as the original material and will give some chance of achieving uniform seals. Peel tabs must be of a size and shape that allow a quick and easy grip by users who are wearing gloves and who are frequently in a hurry. It is therefore important to consider the effect of sharp corners or a change in peel direction; the need to apply a higher peeling force may result in the product flying out of the pack when it is opened.

Shrinkage of the plastic web after forming can lead to the pack becoming distorted after separation from the web — a frequent occurence that can also interfere with ease of peeling and adversely affect the quality of the seal.

From the above, a list of parameters that need consideration when designing a thermoformed pack can be produced:

- Product support (if necessary).
- Sterilization method: does the lidding need to be gas permeable, high-heat resistant, or radiation resistant?
- Tool design for forming the tray: female is preferable to male, and vacuum, pressure, and plug-assist methods are all suitable. A sealing system should be chosen that ensures easy peeling and a uniform seal.
- Likely transit and storage method.

Overall, the blister pack is an efficient and effective method of packing, as long as the time cost and the customer are always considered.

The pouch pack. The choice of pouch packs is between those produced on premade pouch-filling lines and those produced on packing machine form-and-fill systems. (See Figure 3.) The ultimate decision as to which system should be used is generally made on the basis of batch sizes and the number of product changes per day.

The premade pouch system can be set up quickly between product changes, and the capital cost of the system is low. The system can accommodate smaller pack sizes, especially smaller pack widths, than those accommodated by the machine form-and-fill system, but throughput is slow. By comparison, the capital cost of

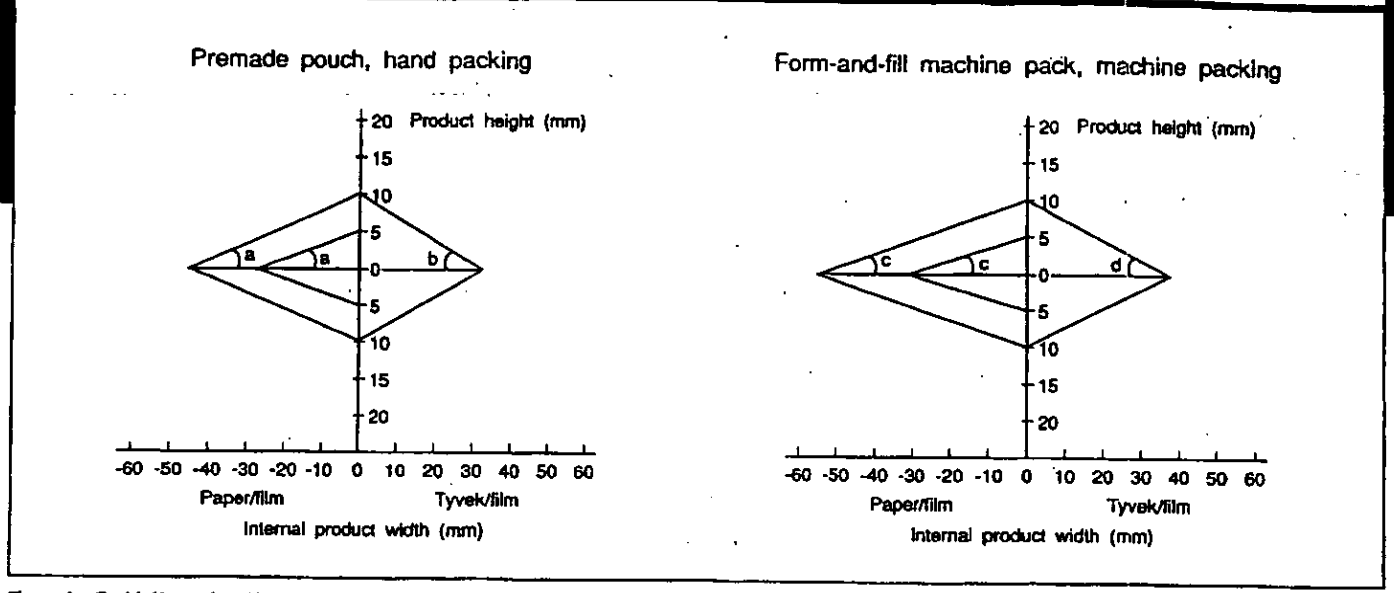


Figure 4. *Guidelines for dimensions of premade pouch and form-and-fill machine pouch. A = 13°, B = 17°, C = 11°, and D = 15°.*

machine form-and-fill systems is high; changeover between products is slow, but throughput is fast.

Consequently, for multi-product-size, low batch-size packaging conditions, the premade pouch can be effective. Packing lines can be streamlined with air-assisted opening and rotary-sealing functions. The premade pouch is less effective, however, for a single-pack size with runs of approximately 2 m/annum, in which case the machine form-and-fill system becomes more effective.

Figure 4 sets out guidelines that can be used when undertaking cost estimates, machine estimates, or when preparing sample packs before the product development engineer has produced a product mock-up. The pouch length can be assessed in order to give the same distance between product and cross seals. The dimension can be used for paper weight between 59 gm^{-2} and 100 gm^{-2}, coated or uncoated, and Tyvek weighing 61–75 gm^{-2}, coated or uncoated.

The difference between coated paper and coated Tyvek reflects the contrast between the adhesive coatings that can be used on these two materials; Tyvek displays a far stronger bond than paper if the correct adhesive coating is used. A similar difference can be seen with latex reinforced paper.

The difference in material weight within the same substance category affects the burst-strength and tear-strength levels of a package, therefore allowing for heavier weights and larger packs with the same seal strength and peel strength.

The main factors affecting the pouch design tend to be the same whether for premade or machine form-and-fill pouches. It is essential to keep a balance between the two webs, and the stiffness of the film layer should respond to the stiffness of the paper or Tyvek layer.

The pouch should always be designed so as to allow it to be peeled open from both webs with equal force because if the film side is made flimsier than the paper side, the peeling force will be biased and will affect the angle of peel. Measurement of the same seal at varying angles should show that the nearer the person opening the pack can get to achieving a 90° separation angle, the easier it is to open and the less likelihood there is of tearing the paper surface or causing fibre lift. This problem doesn't occur with Tyvek sealed to film.

The tendency to seal down the peel flap is a source of constant irritation to users and can be controlled with inspections and suitable specification controls for machine settings. The peel flap is frequently made smaller as the pouch size reduces, but packaging engineers should remember that the end user remains the same size and often has gloves on.

The peel strength of long, narrow pouches should be reduced relative to wide, rectangular pouches. This can be done by reducing the seal width, bearing in mind that the minimum seal width required for a grid-patterned lacquer must allow for at least two lines of adhesive. Allover coatings can be tailored more closely. Peel strength versus seal strength is also an important consideration in respect of sterile pouches and should be engineered in such a way as to suit both the sterilization stresses and the mechanism of opening.

The edge of the seal is frequently stronger than the main body of the seal due to sharp right angles on the edge of seal profiles. Narrow pouches overcome this with the chevron lead-in that reduces the force required to peel open the pouch while still retaining the seal strength from internal strain. Very wide pouches do not offer this advantage so readily. (See Figure 5.) This can lead to excessive effort when initiating the peel, followed by a jerky response with the follow-on.

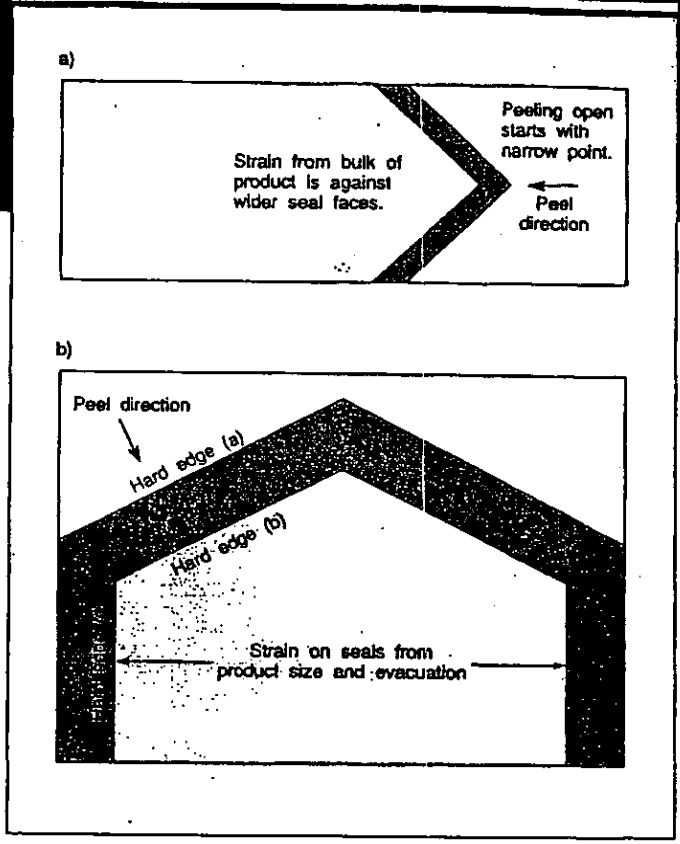


Figure 5: *a) Schematic representation of chevron lead-in. b) Schematic representation of chevron lead-in on wide pouch. Hard edge (a) causes difficulty at initiation; hard edge (b) can cause fibre lift when seal strength is above level of fibre tear; hard edge (c) can be beneficial against strain from product or evacuation.*

The trailing or inner edge of the cross seal can produce the same jerking effect as the seal opens. The level of seal can overcome the mechanical strength of paper fibres and lead to tear or fibre lift, a solution being to round off the profile edges of cross seals. Side seals, on the other hand, can benefit from a stronger edge to the seal, as this is the direction of strain exerted by the bulk of the product or by the ballooning effect during evacuation.

The bag pack. The straightforward polyethylene bag used for the packaging of garments and drapes is traditional and inexpensive, but the opening techniques for the user are not always satisfactory.

The weak or stressed line across the bag is very difficult to engineer in such a way that the same degree of force is required for opening from bag to bag, and the snap-top effect needs practice and leaves a nonsterile edge in contact with the product. The header or breather bag idea, however, is more effective because it is a combination of the easy-to-handle polythene bag and the easy-to-open peel pouch. The advantages of this kind of pack are threefold:

- bulky items can be held in tight packs because the side seals are welded,

- the opening technique is the same as for a pouch (i.e., peeling from a flap), and
- when the peel flap is removed it exposes the product, which can be extricated without contamination from nonsterile surfaces.

The packing technique for bags can be improved and quickened by the use of a bag-opening system such as the About Packaging Pouchmaster PacSystem (Acorn Equipment, Stanmore, United Kingdom) already used in the medical device field. Packaging units can also be set up that produce light airflow to open the bag, which can frequently be the lengthiest activity with polyethylene bags. Excess material is removed when the bag is sealed.

THE SHELF/MULTIUNIT CONTAINER

The cartoning of medical devices appears to have turned full circle between the 1970s and the 1990s. In the 1970s, cartons tended to be made from white-lined chipboard or other forms of glossed, folding boxboard to give at least the appearance of cleanliness and sterility. The late 1970s and the early 1980s saw the introduction of "E" Flute corrugated board designed to provide better support and lower cost. Device cartoning in the 1990s is dominated by "E" Flute, but price increases have been so great as to once again make chipboard more economical and, therefore, more attractive.

Whichever material is used, the carton must protect and inform. It must protect the product and unit pack through sterilization and during a five-year shelf-life. It must inform the hospital personnel of its exact contents, the manufacturer's details, the batch-tracing numbers, and the date of expiry; and it must assist storeroom personnel by allowing easy stacking and removal of the product.

There are a number of guidelines in relation to cartoning medical devices that should be considered: pack from the wide side because it is quicker and easier; dispense through the narrow side; store with the smallest dimension along the shelf; and stack on the ends so the board is at its strongest.■

Robin Lewis, M. Inst. Pkg., holds multiple positions within Perfecseal Ltd., Branch Office, Stodmarsh Road, Canterbury, Kent CT3 4AG, United Kingdom tel. 0227 472093, fax 0227 472824.

Medical Device Technology's Director of Regulatory Affairs

Aster Publishing Corporation and *Medical Device Technology* are pleased to announce that Doris J. Bates, PhD, has joined the company as Director of Regulatory Affairs. In this capacity, Bates will act as a staff consultant and adviser, drawing upon her seven years of experience in the pharmaceutical industry. In addition, she will actively contribute to meeting our readers' needs for timely information concerning developments in regulatory affairs, clinical research, and related areas. Bates received her BS in Biochemistry in 1977 from the University of Maryland, College Park, Maryland; her MA in 1979 from Brandeis University, Waltham, Massachusetts; and her PhD in Organometallic Chemistry in 1984 from Brandeis.

Beginning in 1983 as senior scientist/scientific writer at Sandoz Pharmaceuticals in East Hanover, New Jersey, Bates was responsible for reviewing and editing drug master files and INDs (focusing on chemical synthesis, structure proof, and analytical controls). Later, as manager of technical operations coordination at Sandoz, Bates was responsible for reviewing, submitting, and following up chemistry, manufacturing, and controls-related supplemental submissions, as well as reviewing the chemistry sections of original NDAs, ANDAs, and AADAs and working extensively with DMFs and VMFs.

In 1988 Bates joined Bristol-Myers in Syracuse, New York, as manager of chemistry/pharmacy regulatory affairs. She was responsible for producing, reviewing, submitting, and following up the chemistry, manufacturing, and controls sections of INDs, IND amendments, IND annual reports, NDAs, and NDA amendments, as well as CTA, CTX, and PLA submissions in the United Kingdom.

In 1989 Bates moved to Fisons in Rochester, New York, as senior manager of international regulatory affairs. This move involved a six-month assignment in the firm's Loughborough, U.K., office, where Bates was active in international clinical trials applications and PLAs, primarily involving EEC and EFTA countries. On her return to the United States, she assumed responsibility for organizing and supervising the company's International Regulatory Affairs Department.

Bates's experiences — beginning with domestic regulatory and clinical matters and progressing to international matters — make her a valuable resource for the Editorial and Conference divisions of *Medical Device Technology*.

–The Editor

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.: 37697-0033

Applicant(s):	Edward W. MERRILL *et al.*	Confirmation No.: 8881
Serial No.:	09/764,445	Examiner: D. Truong
Filing Date:	January 19, 2001	Group Art Unit: 1711
Title:	RADIATION AND MELT TREATED ULTRA HIGH MOLECULAR WEIGHT POLYETHYLENE PROSTHETIC DEVICES	

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR §1.56 and 37 CFR §1.97

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

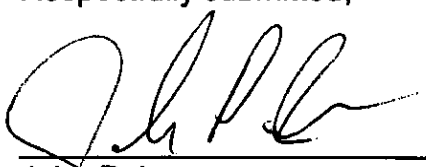
Submitted herewith on Form PTO/SB/08A is a listing of documents known to applicants in order to comply with applicants' duty of disclosure pursuant to 37 C.F.R. §1.56 and §1.97. A copy of each of the listed documents are being submitted to comply with the provisions of 37 C.F.R. §1.97-1.99.

The submission of any document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application or is considered to be material to patentability as defined in 37 C.F.R. §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a *prima facie* prior art reference against the claims of the present application.

Applicants believe that the instant Information Disclosure Statement is being filed within three months of the filing date under 37 CFR §1.97(b)(1), therefore, no fee is required in connection with its filing.

Applicants respectfully request that the listed documents be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08A be returned in accordance with M.P.E.P. §609.

Respectfully submitted,



October 8, 2003
Date

John P. Isacson
Attorney for Applicant
Reg. No. 33,715

HELLER EHRMAN WHITE & MCAULIFFE
1666 K Street, N.W., Suite 300
Washington, DC 20006
Phone: (202) 912-2000
Fax: (202) 912-2020
Customer No. 26633